UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/714,574	11/14/2003	Jeffrey M. Isner	47624-DVC (71417)	1777

7590 07/10/2006

Edwards & Angell, LLP
Intellectual Property Practice Group
P.O. Box 55874
Boston, MA 02205

EXAMINER	
NGUYEN, QUANG	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 07/10/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/714,574	**Applicant(s)** ISNER ET AL.	
	Examiner Quang Nguyen, Ph.D.	**Art Unit** 1633	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 26 June 2006 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires _____months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☒ The Notice of Appeal was filed on *6/26/06*. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☒ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☒ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☒ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: *See Continuation Sheet*. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *49-61 and 63-66*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____
13. ☐ Other: _____.

Continuation of 3. NOTE: The scope of new claims 67-72 in the proposed amendment is not the same as that of the finally rejected claims. Therefore, the proposed new claims would require further consideration (e.g., a new priority date) and a new search .

Continuation of 11. does NOT place the application in condition for allowance because: Applicant's arguments are respectfully found not persuasive for the following reasons.

1. With respect to Priority claim, Applicants argued that the scope of the invention described in the provisional '262 application is not limited to GM-CSF, but extends to virtually any cytokine as evidenced by the statement "cytokine-induced EPC mobilization can enhance neovascularization in both severe tissue ischemia, as well as de novo (sic) vascularization of previously avascular tissues" (page 13, lines 13-15), and that methods for identifying such factors are described in the '262 application, as evidenced at pages 12-13. Applicants further argued that the statement "an angiogeneic factor can be combined with other genes or their encoded gene products to enhance the activity of targeted cells,while simultaneously inducing angiogenesis", and a list of exemplary angiogenic factors that are useful for the methods is provided on page 8, lines 6-16.

Please note that none of the above cited statements indicated or even suggested that at the filing date of the provisional '262 application (3/9/1998), Applicants contemplated to use specifically SCF or any colony stimualting factor (CSF) other than GM-CSF to induce EPC mobilization. It should also be noted that there are numberous members in a broad genus cytokine family, and the induction of EPC mobilization is not necessarily a property of a cytokine. Similarly, most angigogenic factors are not capable of inducing EPC mobilization. Pages 12-13 described basically that GM-CSF is a potent stimulus for EPC mobilization. It is further noted that title of the provisional application is "GM-CSF induced EPC mobilization".

2. With respect to the 103(a) rejection over Isner in view of Hammond et al., Applicants presented similar arguments as those in the Amendments filed on 11/4/05 which were found to be unpersuasvie (see Office action mailed on 1/25/06, pages 6-8). Once again, Applicants argue basically that Hammond describes methods for coating a synthetic vascular graft, endothelial coatings of synthetic materials to reduce thrombus formation and not enhancing endothelialization in a tissue of a patient. Additionally, Applicants argue that the endothelialization results obtained by Hammond fail to provide the requisite motivation to combine or the expectation of success because of the undesired side effects that could affect the long-term utility of the BMB grafts reported in example 1. Furthermore, Applicants argue that Hammond fails to teach or suggest any method for treating myocardial ischemia in a tissue of a subject, much less the presently claimed invention.

Please note that this is a 103 rejection, and it appears that Applicants ignored completely the teachings of Isner. Isner teaches clearly that an angiogenic factor can be combined with other genes or their encoded gene products to enhance the activity of targeted cells in a method for enhancing blood vessel formation or angiogenesis in an ischemic tissue, including ischemic cardiomyopathy or myocardial ischemia, in a mammal. Hammond et al. teaches clearly that SCF, GM-CSF, G-CSF are capable of mobilizing bone-marrow derived endothelial cell progenitors or non-adherent CD34+ cells in the blood for enhancing the endothelialization of synthetic vascular grafts in a patient. Hammond et al. also notes that CD34+ circulating cells in the blood can participate in the repair of ischemic tissue (col.3, lines 28-37). As already noted in the final rejection mailed on 1/25/06, an ordinary skilled artisan would have been motivated to modify the method of Isner by further administering to the treated mammal an effective amount of at least one of SCF or CSF or an effective fragment thereof because Hammond et al. already demonstrated that the aforementioned cytokines are capable of mobilizing bone-marrow derived endothelial cell progneitors or non-adherent CD34+ cells in the blood, and that this mobilization of endothelial cell progenitors would further enhance blood vessel formation or angiogenesis in an ischemic tissue in a mammal having a myocardial ischemia, and thus further optimizing the angiogenic therapeutic outcome. With respect to the undesired side effects in example 1, please note that BMB grafts were seeded with autologous bone marrow blood (BMB) ex vivo prior to their implantation in vivo, these undesired side effects were not observed in animals receiving G-CSF after the implantation of the graft (see at least examples 3 and 4). Thus, there is no teaching away whatever in the reference of Hammond et al., particularly on the main issue that SCF,GM-CSF and G-CSF are capable of mobilizing bone-marrow derived endothelial cell progenitors or non-adherent CD34+ cells in the blood for enhancing endothelialization. Furthermore, Applicants failed to provide a reasonable rational why this particular teaching would have no expectation of success.

3. With respect to the 103(a) rejection over Isner in view of Bussolino et al., Applicants argued that Bussolino shows that G-CSF has only a weak effect in vivo, and that the weak angiogenic activity described in Bussolino would be insufficient to motivate the skilled artisan to adapt the method taught by Isner to include G-CSF, particularly G-CSF was less active than bFGF. Applicants further argued that Bussolino fails to conclude that G-CSF and bFGF exhibit a synergistic effect, but rather Bussolino states that the observed effects were merely suggestive of a cooperative effect, and fails to conclusively determine the nature of the interaction between bFGF and G-CSF. Applicants also argued that Bussolino emphasizes the preliminary nature of the G-CSF and bFGF results and that Bussolino teaches that it is difficult to predict effects on in vivo angiogenesis.

Please note that the results of Bussolino et al. indicated clearly that G-CSF is an angiogenic factor, although its activity is weak relative to bFGF; and that the combination of bFGF and G-CSF resulted in an angiogenic response in vivo that might be a co-operative interaction or a synergistic effect of these two cytokines. Regardless of the nature of the interaction, an unexpected angiogenic response was obtained by combining non-angiogenic doses of bFGF and G-CSF in vivo. Therefore, the further administration of these cytokines would also result in an enhanced angiogenesis in the ischemic tissue, at least through an additive effect or other effects including the synergistic effects of bFGF and G-CSF suggested by Bussolino. Isner already taught the delivery of a nucleic acid encoding an angiogenic protein such as bFGF, GM-CSF, CSF or M-CSF to enhance blood vessel formation or angiogenesis in an ischemic tissue in a mammal, then why is it unpredictable that the further administration of at least G-CSF, bFGF would not result in the formation of a new blood vessel, particularly in light of the teachings of Isner and Bussolino et al. Once again, it appears that Applicants ignored completely the teachings of Isner. Furthermore, please note that colony stimulating factor (CSF) in the claims encompasses G-CSF; and

that Bussolino et al. also taught that both GM-CSF and G-CSF are capable of inducing endothelial cells to proliferate and migrate in vitro.

4. With respect to the Provisional Double Patenting Rejection, it is maintained because the instant claims were not allowed and/or no terminal disclaimer was filed.

Finally, with respect to Applicant's arguments directed to new claims, they were not considered because the new claims were not entered for the reasons set forth above.

QUANG NGUYEN, PH.D
PATENT EXAMINER